

PATENT SPECIFICATION

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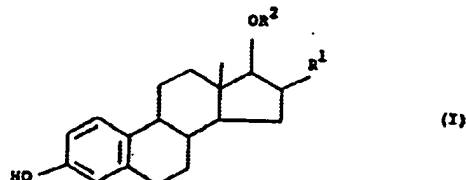


(54) ESTRADIOL DERIVATIVES

(71) We, TAKEDA YAKUHI KOGYO KABUSHIKI KAISHA, also known as TAKEDA CHEMICAL INDUSTRIES LTD., of 27 Doshomachi 2-chome, Higashi-ku, Osaka, Japan, a body corporate organised under the laws of Japan, do hereby declare the invention, for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—

The present invention relates to novel and useful 16 β -alkylestradiol derivatives and to a process for producing them.

More particularly, the present invention relates to 16 β -alkylestradiols represented by the formula (I):



wherein R¹ is an alkyl group or an alkenyl group of two or more carbon atoms; and R² is hydrogen or an acyl group (as herein defined), and to a process for producing the compounds (I).

Hitherto, testosterone or derivatives thereof (e.g. testosterone propionate) have been introduced for the therapy of estrogen-dependent disease (e.g. advanced breast cancer) as antiestrogen drugs. However, the therapy is generally accompanied with the drawback *inter alia* that the virilizing effect resulting from the androgenic potency of testosterone prevents the patient from continuing with the therapy.

We have discovered that 16 β -alkylestradiol derivatives have substantially no estrogen activity but rather have an antiestrogen activity, and that this propensity is particularly pronounced where the number of carbon atoms in the 16 β -alkyl moiety is within the range of from 2 to 4. The present invention is accomplished on the basis of these findings.

The present invention provides compounds of the general formula (I), which are useful as an antiestrogen drug, and a process for producing the compounds (I).

Referring to the formula (I) and to formula (II) described below, the alkyl group or alkenyl group of two or more carbon atoms designated by R¹ may be straight-chain or branched, and saturated or unsaturated, thus being exemplified by lower alkyl groups having 2 to 4 carbon atoms, such as ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, tert-butyl, allyl and 3-butenyl. The acyl group designated by R² in formula (I) above and by R² and R³ in formula (II) below is defined as a hydrocarbon-carbonyl group whose hydrocarbon moiety has from 1 to 8 carbon atoms. The hydrocarbon-carbonyl group is exemplified by lower alkylcarbonyl groups whose alkyl moieties have 1 to 3 carbon atoms, e.g. acetyl, propionyl, butyryl; arylcarbonyl groups, e.g. benzoyl; and aralkylcarbonyl groups, e.g. phenylpropionyl. Where R² and R³ are an acyl group, the substituent —OR² or —OR³ in the 17-position of formula (I) or (II) is an esterified hydroxyl group, and the corresponding compound is a 17-ester of the compound (I) or (II). The